

IN THE CLAIMS

Please amend claim 1 as follows:

1. (Twice Amended) A method of treating sexual dysfunction which comprises administering to a subject suffering therefrom and in need of treatment an effective amount of a bombesin receptor antagonist.

Please amend claim 16 as follows:

16. (Amended) The method of Claim 1, wherein the bombesin receptor antagonist is administered in combination with L-arginine or a PDE 5 inhibitor.

Please amend claim 19 as follows:

19. (Amended) The method of claim 1, which comprises administering to a subject a bombesin receptor antagonist in combination with a second agent comprising catecholamine agonist, a 5HT<sub>2</sub> antagonist, a monoamine synthesis modifier, or a monoamine metabolism or uptake modifier useful for the treatment of sexual dysfunction.

Please amend claim 20 as follows:

20. (Amended) The method of claim 19, wherein the second agent is selected from quinelorane, ritanserine, para-chlorophenylalanine or imipramine.

Please amend claim 23 as follows:

23. (Amended) The method of claim 19 wherein the bombesin receptor antagonist and the catecholamine agonist, 5HT<sub>2</sub> antagonist, monoamine synthesis modifier, or monoamine metabolism or uptake modifier are simultaneously administered to the subject in the form of a composition containing a unit dose of the bombesin receptor antagonist, a unit dose of the catecholamine agonist, 5HT<sub>2</sub> antagonist, monoamine synthesis modifier, or

monoamine metabolism or uptake modifier and a pharmaceutically acceptable carrier or diluent.

Please Cancel Claim 32.

Please amend claim 33 as follows:

33. (Amended) The method of claim 5, wherein the bombesin receptor antagonist is administered to the subject in combination with an angiotensin-2 receptor antagonist.

Please amend claim 36 as follows:

36. (Amended) The method of claim 5, wherein the bombesin receptor antagonist is administered to the subject in combination with a catecholamine agonist or 5HT<sub>2</sub> antagonist.

Please Cancel Claim 43.

Please amend claim 44 as follows:

44. (Amended) The method of claim 6, wherein the bombesin receptor antagonist is administered to the subject in combination with an angiotensin-2 receptor antagonist.

Please amend claim 46 as follows:

46. (Amended) The method of claim 6, wherein the bombesin receptor antagonist is administered to the subject in combination with a catecholamine agonist, 5HT<sub>2</sub> antagonist.,

REMARKS

Applicants respectfully request entry of the amendments hereinabove, reconsideration of the Office Action mailed on February 12, 2003 and allowance of the claims.

It is requested that the references listed on that previously submitted form PTO-FB-A820 be included in the "References Cited" portion of any patent issuing on this application (M.P.E.P. 1302.12).

Applicants wish to thank Examiner San-ming Hui for acknowledging the claim for domestic priority.

While Applicants submit that they have claimed priority from the parent applications as acknowledged in the December 3, 2001 Filing Receipt for the above-identified application, out of an abundance of caution, Applicants also include a Petition pursuant to 37 C.F.R. §1.78(a)(3) and a copy of this Amendment (under separate cover) herein amending the above-identified application to claim priority.

The rejection states "*The amendments filed October 30, 2002 have been entered.*

*The cancellation of claims 2-3, 11-13 and 15 is acknowledged. The addition of claims 24-46 is acknowledged.*

*Claims 16 and 43 are objected to because of the following informalities: the use of abbreviation in claim 16: "NO" and claim 43, line 2: "VIP enhancer", is considered improper. Appropriate correction is required.*

Applicants have herein replaced the term NO with "L-Arginine or a PDE inhibitor" thus obviating the objection. Applicants have herein cancelled the claims directed to VIP enhancers thus obviating the rejection.

Claims 1, 4-10, 14 and 16-46 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The rejection states the claims are drawn to a method of "preventing sexual

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dysfunction". The rejection states in the instant specification, there is no guidance as to how one skilled in the art to select an appropriate bombesin receptor antagonist in use for "preventing the sexual dysfunction". The rejection states the instant specification only discloses embodiments to "treat" sexual dysfunction rather than "prevent" it. The rejection states working examples in demonstrating the preventive efficacy of bombesin antagonist in the method of preventing sexual dysfunction are not disclosed in the instant specification. The rejection states it is well-known in the art that sexual dysfunction can be caused by various different etiologies (See Merck Index reference of record) and none of those etiologies are known to the skilled of artisan to be directly associated with bombesin receptor. The rejection states without specific guidance in the specification, under experimentation would be required for one of skilled in the art to ascertain the appropriate embodiment to "prevent sexual dysfunction".

Applicants have herein amended Claim 1 and accordingly dependent claims 4-10, 14 and 16-46 by deleting the prevention phrase thus obviating the rejection under 35 U.S.C. 112, first paragraph.

Claims 36 and 46 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The rejection states the term "neurotransmitter modulator" recited in the claims encompasses selective serotonin reuptake inhibitor (SSRI). The rejection states however, SSRI are known to cause sexual dysfunction. The rejection states therefore, claims 36 and 46 are not enabled for the full scope as claimed. The rejection states there are only limited numbers of neurotransmitter are set forth in the

instant specification. The rejection states without any specific guidance on how to select and ascertain the appropriate embodiments to practice the instant invention, undue experimentation would be required for one of skilled in the art to ascertain the appropriate embodiment to practice the instant invention.

Applicants have amended claim 19 to recite that the combination agent is a catecholamine agonist, a 5HT<sub>2</sub> antagonist, a monoamine synthesis modifier, or a monoamine metabolism or uptake modifier. Support for this amendment may be found on page 49, lines 20-30. Claims 23, 36 and 46 were amended with an analogous amendment thus obviating the rejection of claims 36 and 46 under 35 U.S.C. 112, first paragraph.

} chart & review

Claims 1, 4-10, 14 and 16-46 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The rejection states the expression "a method of ... preventing sexual dysfunction ... subject ... liable to suffer therefrom" recited in claim 1 renders the claims indefinite as to the host encompassed thereby. The rejection states it is not clear what subjects would be encompassed by the claims because there is not known how to predict sexual dysfunction before it happens.

The rejection states the expression, "a method of preventing sexual dysfunction" in claim 1, line 1, renders the claims indefinite as failing to clearly set forth the metes and bounds of the patent protection desired. The rejection states examples of how and when to prevent sexual dysfunction are not set forth in the specification. The rejection states absent such exemplification, the skilled artisan could not establish the identity of those situations wherein prevention of sexual dysfunction would be effected. The rejection states furthermore, it is

unclear as to the degree of prevention (e.g., total prevention, some prevention, probable prevention, total prevention in most cases...etc.) herein because the specification does not disclose the extent of prevention achieved.

The rejection states the expression "a compound that promotes production of NO" in claim 16 renders the claims indefinite as to the compound encompassed thereby. The rejection states it is unclear what compounds would be considered as "a compound that promotes production of NO".

The rejection states the expression "an angiotensin-2 receptor" in claims 33 and 44 are not clearly understood. The rejection states it is apparent the term is intended to refer to "an angiotensin-2 receptor antagonist". The rejection states if it is so, appropriate correction is recommended.

The rejection states the term "VIP enhancer" in claim 43 renders the claim indefinite as to the compounds encompassed thereby.

Applicants traverse in part the rejection of Claims 1, 4-10, 14 and 16-46 (as amended) under 35 U.S.C. 112, second paragraph.

Applicants have herein amended Claim 1 and accordingly dependent claims 4-10, 14 and 16-46 by deleting the prevention phrase thus obviating the rejection under 35 U.S.C. 112, second paragraph.

Applicants have amended claim 16 to further clarify the invention by reciting certain NO (nitric oxide) enhancers as oxide L-arginine and PDE 5 inhibitors. Support for this amendment may be found on page 49, line 1.

Applicants have herein clarified claims 33 and 44 to recite antiotensin-2-receptor antagonist in accordance with the Examiner's suggestion. Support for this amendment may be found on page 49, line 6.

Applicants have deleted the term VIP enhancer from claims 32 and 43

(i.e. claims 32 and 43 are cancelled).

Applicants have amended claim 19 to recite that the combination agent is a catecholamine agonist, a 5HT<sub>2</sub> antagonist, a monoamine synthesis modifier, or a monoamine metabolism or uptake modifier. Support for this amendment may be found on page 49, lines 20-30. Claims 23, 36 and 46 were amended with an analogous amendment.

Applicants have amended claim 20 by deleting the phrase neurotransmitter agonist or antagonist and replacing it with “second agent”.

Claims 1, 4-9, 24-28 and 37-39 are rejected under 35 U.S.C. 102(b) as being anticipated by Howell et al. (WO 98/07718).

The rejection states that Howell et al. (WO 98/07718) teaches a method of treating and/or preventing depression employing an oral pharmaceutical composition/dosage form comprising non-peptide bombesin receptor antagonists (See particularly, abstract, page 10 and claims 11-12).

Claims 1, 4-9, 24-28, and 37-39 are rejected under 35 U.S.C. 102(b) as being anticipated by Hurel et al., reference of record.

The rejection states that Hurel et al. teaches that bombesin-like peptide antagonists have vasoactive properties, see page 1243.

The rejection states that the method of administering a bombesin antagonist to a patient, whom is liable to suffer, but without sexual dysfunction, will inherently prevent sexual dysfunction in such patient.

The rejection directs Applicants’ attention is directed to *Ex parte Novitski*, 26 USPQ2d 1389 (BOPA 1993) illustrating anticipation resulting from inherent use, absent a *haec verba* recitation for such utility. The rejection states that in the instant application, as in *Ex parte Novitski*, supra, the claims are directed to

preventing a malady or disease with old and well known compounds or compositions. The rejection states that it is now well settled law that administering compounds inherently possessing a protective utility anticipates claims directed to such use. The rejection states that arguments that such protective use is not set forth *haec verba* are not probative. The rejection states that prior use for the same utility clearly anticipates such utility, absent limitations distancing the proffered claims from the inherent anticipated use. The rejection states that attempts to distance claims from anticipated utilities with specification limitations will not be successful. At page 1391, *Ex parte Novitski*, supra, the Board said "We are mindful that, during the patent examination, pending claims must be interpreted as broadly as their terms reasonably allow. *In re Zletz*, 893 F.2d 319, 13 USPQ2d 1320 (Fed. Cir. 1989). As often stated by the CCPA, "we will not read into claims in pending applications limitations from the specification." *In re Winkhaus*, 52 F.2d 637, 188 USPQ 219 (CCPA 1975).". The rejection states that in the instant application, Applicants' failure to distance the proffered claims from the anticipated prophylactic utility, renders such claims anticipated by the prior inherent use.

Applicants traverse the rejection of Claims (as amended) under 35 U.S.C. 102(b) as being anticipated by Howell et al. (WO 98/07718) or Hurel et al. rejection.

The Court of Appeals for the Federal Circuit, in ruling on the standard for anticipation under 35 U.S.C. §102(b), stated

[i]t is elementary that an anticipation rejection requires a showing that each limitation of a claim must be found in a single reference, practice or device.

In re Donohue, 226 U.S.P.Q. 619, 621 (1985); and "...exclusion of a claimed element from a prior art reference is enough to negate anticipation by that reference." Atlas Power Co. v. E. I. duPont DeNemours & Co., 224 U.S.P.Q. 409, 411 (1984).

Applicants submit that the claims as amended are not anticipated by Howell et al. (WO 98/07718) or Hurel et al. since neither reference discloses the use of bombesin antagonists for the treatment of sexual dysfunction. Thus, the treatment of sexual dysfunction is not found in either reference.

Further, inherent anticipation arises when "the prior art necessarily functions in accordance with, or includes, the claimed limitations" (underlining added for emphasis) Atlas Powder Co. v. Ireco Inc., 190 F.3d 1342 (Fed. Cir. 1999). In Glaxo Inc. v. Novopharm Ltd. 34 U.S.P.Q. 2d 1565 (Fed. Cir. 1995) the Federal Circuit affirmed the district court's conclusion that since practicing a prior art Example could yield two different crystals the Example did not anticipate one of those crystals.

Applicants submit that the claims (as amended) are not anticipated due to inherency at least because the prior art does not necessarily function in accordance with, or include, the claimed limitations. In an analogous manner to Glaxo Inc. v.. Novopharm Ltd. supra many patients that suffer from depression do not suffer from sexual dysfunction. Accordingly, it does not follow that the treatment of a patient having depression will necessarily result in the treatment of sexual dysfunction at least because the patient may not have sexual dysfunction.

Claims 1, 4-10, 14 and 16-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Howell et al. (WO 98/07718) and Hurel et al. in view of

Merck Manual and sildenafil prescribing information, references of record.

The rejection states that Howell et al. (WO 98/07718) teaches a method of treating and/or preventing depression employing a oral pharmaceutical composition/dosage form comprising non-peptide bombesin receptor antagonists (see particularly, abstract, page 10 and claims 11-12).

The rejection states that Hurel et al. teaches that bombesin-like peptide antagonists have vasoactive properties (see page 1243).

The rejection admits that Howell et al. (WO 98/07718) and Hurel et al. taken together do not particularly teach the employment of bombesin-like peptide and/or non-peptide antagonists in a method of treating sexual dysfunction. The rejection admits that neither do they teach the combination of vasodilators, neurotransmitter antagonists and/or agonists or a hormone like compound in its method of treating sexual dysfunction.

The rejection states that the Merck Manual teaches depression, low testosterone level and vascular abnormalities as causes of sexual dysfunction (see pages 1575 and 1577-78).

The rejection states that Sildenafil is known as PDE5 inhibitor vasodilator employed in the treatment of sexual dysfunction (see pages 5-6).

The rejection states that it would have been obvious to one of ordinary skill in the art at the time the invention was made to employ bombesin-like peptide and/or non-peptide antagonists in a method of treating sexual dysfunction. The rejection states that it would also have been obvious to combine the bombesin receptor antagonist with vasodilators, neurotransmitter antagonists and/or agonists or a hormone like compound in a method of treating sexual dysfunction.

The rejection reasons that one of ordinary skill in the art would have been motivated to employ bombesin-like peptide and/or non-peptide antagonists in a method of treating sexual dysfunction because (1) they are known to be employed in methods of treating depression which is known to be an underlying cause of sexual dysfunction; (2) they are known to be vasoactive which are known to be useful in treating sexual dysfunction. The rejection reasons that one of ordinary skill in the art would have also been motivated to combine the bombesin receptor antagonist with vasodilators, neurotransmitter antagonists and/or agonists or a hormone like compound in a method of treating sexual dysfunction since they are all known to be useful in treating sexual dysfunction. The rejection also concludes that combining agents that are known to be useful for the same purpose in a combination composition to be sued for the same purpose is known to be within the skill of the artisan and therefore, obvious, see *In re Kerkhoven* 205 USPQ 1069.

Applicants traverse the rejection of Claims 1, 4-10, 14 and 16-23 under 35 U.S.C. 103(a) as being unpatentable over Howell et al. (WO 98/07718) and Hurel et al. in view of Merck Manual and sildenafil prescribing information, references of record.

Initially, Applicants note the admission that Howell et al and Hurel et al. taken together do not particularly teach the employment of bombesin-like peptide and/or non-peptide antagonists in a method of treating sexual dysfunction.

The art of record is insufficient to support a *prima facie* case.

Applicants submit their invention is not “obvious to try”, but even assuming arguendo, that the claims are “obvious to try” that is not the standard

for patentability.

Applicants submit that the art of record and extrapolations therefrom are speculative and do not provide a legally sufficient basis to support a *prima facie* case that the administration of bombesin receptor antagonist inhibitors are useful for the treatment of sexual dysfunction. Further, the art does not provide a reasonable expectation of success, without which Applicants' invention cannot be obvious even if it were "obvious to try" (which is denied).

It is Applicants' position that "obvious to try" is not the standard for patentability, and that the Examiner did not make out a *prima facie* case because, *inter alia* (1) the references provide no effective motivation or suggestion that the administration of bombesin receptor antagonist inhibitors as a class could or would be useful for the reduction of sexual dysfunction and (2) even allowing, *arguendo*, that any such suggestion or motivation is provided, the references provide absolutely no expectation of success. The law is emphatic that "obvious to try" is not the standard for patentability.

"Obvious to try" is NOT the test of obviousness under 35 U.S.C. §103.  
*American Hospital supply Corp. v. Travenol Laboratories, Inc.*, 223 USPQ 577, 582 (Fed. Cir. 1984). The Federal Circuit has explained the proper test:

The consistent criterion for determination of obviousness is whether the prior art would have suggested to one of ordinary skill in the art that this process should be carried out **and would have a reasonable likelihood of success**, viewed in light of the prior art. **Both the suggestion and the expectation of success must be founded in the prior art, not in the applicant's disclosure** (emphasis added).

In re Dow Chemical Co., 5 USPQ.2d 1529, 1531 (Fed. Clr. 1988); Amgen, Inc. v. Chugai Pharmaceutical Co. Ltd. 18 USPQ.2d 1016, 1022-23 (Fed. Cir.), cert. denied, 502 U.S. 856 (1991).

As explained fully in the sections which follow, the art cited by the Examiner, at most, makes it no more than perhaps obvious to explore the area of bombesin receptor antagonist inhibitors generally (e.g., for the treatment of pulmonary hypertension), and this is one of the classic hallmarks of an “obvious to try” rejection:

“The admonition that ‘obvious to try’ is not the standard under §103 has been directed mainly at two kinds of error. In some cases, what would have been ‘obvious to try’ would have been to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful...**In others, what was ‘obvious to try’ was to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it.**”

In re O’Farrell, 7 USPQ2d 1673, at 1681, (Fed. Cir. 1988), emphasis supplied.

It is further noted that “[t]he issue of obviousness is determined entirely with reference to a hypothetical person having ordinary skill in the art. It is only that hypothetical person who is presumed to be aware of all the prior art. The actual inventor’s skill is irrelevant to the inquiry, and this is for a very important reason. The statutory emphasis is on a person of ordinary skill. Inventors, as a class, according to the concepts underlying the Constitution and the statutes that have created the patent system, possess something -- call it what you will - - which sets them apart from the workers of ordinary skill, and one should not go about determining obviousness under section 103 by inquiring into what patentees (i.e. inventors) would have known or would likely have done, faced with the revelations of references. A person of ordinary skill in the art is also presumed to be one who thinks along the line of conventional wisdom in the art and is not one to innovate, whether by patient, and often expensive, systematic

research or by extraordinary insights, it makes no difference which.” Standard Oil Co. V. American Cyanamid Co., 774 F.2d 448, 454 (Fed. cir. 1985).

Further, even if the art is, *arguendo*, viewed as providing the barest of suggestions, it provides no reasonable expectation or likelihood of success. Thus, even if an argument could be made that the art provides a suggestion to explore the use of bombesin receptor antagonist inhibitors generally to treat sexual dysfunction, this amounts, perhaps, to inviting experimentation, i.e., to perhaps making testing bombesin receptor antagonist inhibitors obvious to try, which again is manifestly not the standard for patentability. O'Farrell, supra.

Applicants submit that the Hurel et al. reference does not teach that bombesin-like peptide antagonists have vasoactive properties. Thus, Hurel et al. suggests the mere exploration of the use of bombesin receptor antagonist inhibitors as a treatment of pulmonary hypertension, and this is one of the classic hallmarks of an “obvious to try” rejection. The Hurel et al. reference clearly states that “The preliminary study suggests that these peptides have acute haemodynamic effects in the pulmonary vasculature.....Further studies are required.” Applicants submit that the use of the term “suggests” and the statement that further studies “are required” is the hallmark of a suggestion for the exploration of a scientific area. It does not even provide a reasonable likelihood of success that the one bombesin antagonist tested is a vasodilator since it states that further studies are required. This is not sufficient to make a *prima facie* case.

In addition, Hurel et al. only discloses the testing of one bombesin-like antagonist on one subject. This at most provides the suggestion of trying bombesin like antagonists for the treatment of pulmonary hypertension. One

skilled in the art would not have a reasonable likelihood of success from the testing of one compound since the perceived effect could be caused by some other activity of the compound besides the bombesin antagonist activity. Further, one skilled in the art would not have a reasonable likelihood of success from the testing of one subject since there could have been a variety of complex factors that lead to any perceived result.

It is thus respectfully submitted that the Hurel et al. reference is an article which perhaps supplies some interesting academic research tidbits. The mere mention of the word “pulmonary hypertension” amounts to conjecture or speculation, and most certainly does not provide a “reasonable expectation of success”, even if “obvious to try” (which is denied), as required under US patent law for obviousness. ✓

Further, Applicants submit that Hurel et al. does not provide basis for a general teaching that bombesin-like peptide antagonists have vasoactive properties or act as systemic vasodilators. The reference describes patients suffering from pulmonary hypertension (high blood pressure in the lungs). Hurel et al hypothesized that the bombesin-like peptide GRP has vasoactive properties within the innermost layer of the pulmonary artery (pulmonary endothelium) and that a GRP antagonist might have a beneficial effect. While upon administration of a bombesin antagonist pulmonary systolic and diastolic blood pressure were reduced, there was a rise in systemic blood pressure (see Table). Clearly the suggestion that bombesin receptor antagonists increase systemic blood pressure would not motivate one to use such compounds to treat sexual dysfunction. An increase in systemic blood pressure would teach away from the use of bombesin antagonists to treat sexual dysfunction.

The Hurel et al work is further described in the corresponding Hurel WO96/28214 and US 5650395, copies of which have been previously submitted and have been made of record. Hurel refers in 5650395 at column 1 line 36 onwards to an autonomous endocrine system within the lungs termed the pulmonary neuroendocrine system that had been shown to secrete gastrin-related peptide, and claims the use of a bombesin antagonist *only* in relation to the medical indication of lowering pulmonary systolic pressure. Thus claim 1 of the issued US patent reads:

“A method of lowering the pulmonary systolic pressure of a subject suffering from pulmonary hypertension, said method comprising administering to the subject an amount of a bombesin antagonist, said amount being effective to lower the systolic pressure.”

Thus, at best the Hurel et al. art when taken as a whole may suggest bombesin antagonists are useful for the indication of lowering pulmonary systolic pressure but does not suggest that a bombesin antagonist is effective as a peripheral vasodilator and clearly would not motivate one to use a bombesin antagonist to treat sexual dysfunction.

Even if Hurel et al had provided a general teaching of vasoactive properties (which is denied) that would not lead the skilled person to conclude that the disclosed compound might be used in the treatment of sexual dysfunction. Antihypertensive medications may cause erectile dysfunction either by drug-specific effects or by decreasing the systolic pressure and thereby increasing the intracavernosal penile pressure. This result is especially prevalent in patients with diabetes or hypertension who have an underlying microvascular disease. The *Merck Manual of Geriatrics* comments in Chapter

115, Sexual Dysfunction in Men

([http://www.merck.com/pubs/mm\\_geriatrics/sec14/ch115.htm](http://www.merck.com/pubs/mm_geriatrics/sec14/ch115.htm)):

“About 25% of cases of erectile dysfunction are caused by drugs ... especially antihypertensives (most notably reserpine,  $\beta$ -blockers, guanethidine, and methyldopa) ...”

As a further example, benzazepril (Captopril), which is an ACE inhibitor used for the treatment of high blood pressure and congestive heart failure, may give rise in men to reduced libido and more rarely impotence (see <http://www.healthcentral.com/mhc/top/001803.cfm>).

Applicants acknowledge the Examiner’s response to Applicants’ previous arguments regarding antihypertensive agents(see page 11 of instant office action). While Applicants submit that the admitted causation of sexual dysfunction by a variety of antihypertensive drugs (as known in the art) may not have guaranteed that bombesin antagonists would cause sexual dysfunction, such knowledge would certainly have raised a serious question to one skilled in the art whether bombesin antagonists may cause sexual dysfunction (thus negating any reasonable likelihood of success that bombesin antagonists would be useful for the treatment of sexual dysfunction). Again, the case law described above mandates that a reasonable likelihood of success is a necessary element of a *prima facie* case.

Finally, clearly, Hurel et al. does not mention or suggest in any way the treatment of sexual dysfunction.

The Howell et al. published application discloses a method of treating depression. However, since many antidepressants have an adverse effect on

sexual function a disclosure that a group of compounds is effective for the treatment of depression does not disclose or suggest that they would be effective for the treatment of sexual dysfunction. Instead, it teaches away from the use for the treatment of sexual dysfunction. This hardly constitutes the motivation to try other antidepressants for the treatment of sexual dysfunction or that there would be a reasonable likelihood of success that bombesin receptor antagonist inhibitors would be effective for the treatment of sexual dysfunction.

The rejection responded to the Applicants' previous response stating that "only certain classes of antidepressants will cause sexual dysfunction, such as SSRI, and the newer generation of tricyclic antidepressants" and "Absent any evidence that Bombesin antagonists will interact with those neurotransmitter systems, one would still be motivated to employ bombesin antagonists to treat depression and thereby treat sexual dysfunction secondary to depression"

Applicants submit that while the fact that antidepressants may cause sexual dysfunction does not prove or guarantee that Bombesin antagonists may cause sexual dysfunction it certainly raises a serious question whether Bombesin antagonists may cause sexual dysfunction (thus negating any reasonable likelihood of success that bombesin antagonists would be useful for the treatment of sexual dysfunction). Restated, the fact that certain classes of antidepressants will cause sexual dysfunction clearly does not provide a reasonable likelihood of success that Bombesin antagonist antidepressants would be useful for the treatment of sexual dysfunction (in fact it suggests the opposite) . Again, the case law described above mandates that a reasonable likelihood of success is a necessary element of a prima facie case.

Further, the knowledge that bombesin antagonists are antidepressants

coupled with the knowledge that antidepressants cause sexual dysfunction suggests that bombesin antagonists may cause sexual dysfunction. This clearly contradicts the rejection reasoning that one would be motivated to employ bombesin antagonists in a method of treating sexual dysfunction because they are known to be employed in methods of treating depression which is known to be an underlying cause of sexual dysfunction. Applicants submit that the inference that bombesin antagonists may cause sexual dysfunction clearly negates the motivation suggested in the rejection.

Claims 24-46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Howell et al. (WO 98/07718) and Hurel et al. in view of Merck Manual and sildenafil prescribing information, references of record as applied to claims 1, 4-10, 14 and 16-23 above, and further in view of Leiblum (International Journal of Impotence Research, 1998, 10(Suppl 2): S104-S106), Levin (Exp. Clin. Endocrinol., 1991;98(2):61-69), Gioco et al. (US Patent 5,565,466).

The rejection states that Leiblum teaches different sexual disorders are affected by either mood disorder such as depression, which would reduce the desire of sexual activities, or vascular factors such as decreased vaginal lubrication which can cause pain during intercourse and female arousal disorder (see particularly page S105, col. 1, second paragraph - col. 2 and pages S106, col. 1).

The rejection states that Levin teaches VIP can increase the vaginal lubrication and induce arousal in female patients (see particularly the abstract).

The rejection states that Gioco et al. teaches a method of modulating the excitatory phase of male and female sexual response using vasodilating agents such as phentolamine, yohimbine,  $\alpha$ -adrenergic vasodilator, and imipramine

(See col. 12, line 11 to col. 13, line 31, 45, and 66, Examples 3 and 4; also particularly claims 14 and 17).

The rejection reasons that it would have been obvious to one of the ordinary skill in the art at the time the invention was made to combine the herein secondary agent with bombesin antagonist in a method of treating sexual dysfunction.

The rejection reasons that one of ordinary skill in the art would have been motivated to combine the herein secondary agents with bombesin antagonist in a method of treating sexual dysfunction because various sexual dysfunction are known to be affected by various factors such as depression and vascular. The rejection reasons that combining the herein claimed secondary agents, which are known to correct and treat the under lying conditions that negatively affect sexual activities individually, with bombesin antagonist into a single composition for the very same purpose would be obvious (see *In re Kerkhoven* 205 USPQ 1069), absent evidence to the contrary.

Applicants traverse the rejection of Claims 24-46 (as amended) under 35 U.S.C. 103(a) as being unpatentable over Howell et al. (WO 98/07718) and Hurel et al. in view of Merck Manual and sildenafil prescribing information, references of record as applied to claims 1, 4-10, 14 and 16-23 above, and further in view of Leiblum (International Journal of Impotence Research, 1998, 10(Suppl 2): S104-S106), Levin (Exp. Clin. Endocrinol., 1991;98(2):61-69), Gioco et al. (US Patent 5,565,466).

Applicants submit that, at least for the reasons provided above in response to the rejection of claim 1 and dependent claims thereof, claims 24-46 (as dependent claims) are not obvious in light of the plethora of references cited

by the rejection. Applicants further note that the rejection of claims 24-46 relies upon at least 5 references in combination and as many as 7 references in combination and Applicants submit that such a multiplicity of a combination of references appears to be based upon the impermissible use of hindsight.

Attached hereto is a "Version with Markings to Show Changes Made."

Please charge any additional fees which may be required, or credit any overpayment, to Deposit Account No. 16-1445. Two copies of this sheet are enclosed.

Date: 4/14/2003

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#57512 v1 - PC17351 AMENDMENT